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# **Guidance for Industry**

## **Pediatric Study Plans:**

### **Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans**

#### ***DRAFT GUIDANCE***

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For questions regarding this draft document contact (CDER) Rosemary Addy at 301-796-1640 or (CBER) the Office of Communication, Outreach, and Development at 301-827-1800 or 800-835-4709.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**July 2013  
Procedural**

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### **Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans**

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**U.S. Department of Health and Human Services  
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**Guidance for Industry<sup>1</sup>**  
**Pediatric Study Plans: Content of and Process for**  
**Submitting Initial Pediatric Study Plans and**  
**Amended Pediatric Study Plans**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**I. INTRODUCTION**

The purpose of this draft guidance is to assist sponsors in the submission of an initial pediatric study plan (PSP) and any amendments to the PSP. Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding implementation of the requirement for sponsors to submit an initial PSP as described in section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA).<sup>2</sup>

This draft guidance addresses the following topics:

- Who must submit an initial PSP
- When an initial PSP must be submitted
- What should be included in an initial PSP
- What should be included in a requested amendment to an agreed-upon initial PSP
- A template that should be used for an initial PSP submission<sup>3</sup>

<sup>1</sup> This guidance has been prepared by the Pediatric Study Plan Working Group, composed of members from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Office of the Commissioner (OC) at the Food and Drug Administration.

<sup>2</sup> Public Law 112-144, 126 Stat. 993 (July 9, 2012)

<sup>3</sup> In addition to consulting guidance, sponsors are encouraged to contact the specific CDER/CBER review division or the Pediatric and Maternal Health Staff to discuss specific issues that arise during preparation of the initial PSP.

## *Contains Nonbinding Recommendations*

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This draft guidance does not contain a discussion of general requirements for pediatric drug development under the Pediatric Research Equity Act (PREA).<sup>4</sup> That topic is addressed in the draft guidance for industry *How to Comply With the Pediatric Research Equity Act*.<sup>5</sup>

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## **II. BACKGROUND**

Over the last 2 decades, the FDA has worked to address the problem of inadequate pediatric testing and inadequate pediatric use information in drug and biological product labeling. In 1994, the FDA published a final rule that required manufacturers of marketed drugs to survey existing data and determine whether those data were sufficient to support adding pediatric use information to the drug's labeling.<sup>6</sup> However, the 1994 rule did not impose a general requirement that manufacturers carry out studies when existing information was not sufficient to support adding pediatric use information. This initial attempt to encourage sponsors to submit pediatric studies and plans to sufficiently inform use of drugs in pediatric patients was not successful in achieving adequate labeling for most drugs and biological products for use in the pediatric subpopulation, and product labeling frequently failed to provide directions for safe and effective use in pediatric patients.

To address this continued problem, in 1997 the Food and Drug Administration Modernization Act of 1997<sup>7</sup> was signed into law and contained provisions that established incentives for conducting pediatric studies on drugs for which exclusivity or patent protection exists. Also, on December 2, 1998, the FDA published a regulation known as the pediatric rule.<sup>8</sup> This rule partially addressed the lack of pediatric use information by requiring manufacturers of certain new and marketed drugs and biologics to conduct studies to provide sufficient data and information to support directions for pediatric use for the claimed indications. The pediatric rule also stated that the FDA would provide sponsors with its best judgment on whether pediatric

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<sup>4</sup> For purposes of this guidance, references to *drugs* and *drug and biological products* include drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological drug products licensed under 351 of the Public Health Service Act (42 U.S.C. 262).

<sup>5</sup> When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>6</sup> See "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling" (59 FR 64240, December 13, 1994).

<sup>7</sup> Public Law 105-115, 111 Stat. 2296 (Nov. 21, 1997)

<sup>8</sup> See "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients" (63 FR 66632, December 2, 1998).

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studies will be required and whether their submission will be deferred until after approval. This input was given by the FDA at the end-of-phase 1 meeting, for drugs and biologics for life-threatening diseases, and at the end-of-phase 2 meeting, for other drugs, as described in other FDA regulations.<sup>9</sup>

The pediatric rule also stated that sponsors should submit, at least 1 month in advance of the end-of-phase 2 meeting, certain background information, including a proposed timeline for protocol finalization, enrollment, completion, and data analysis, or, in the alternative, information to support a planned request for waiver or deferral. However, on October 17, 2002, the U.S. District Court for the District of Columbia held that the FDA had exceeded its statutory authority when issuing the pediatric rule and the court suspended its implementation and enjoined its enforcement.<sup>10</sup>

Congress subsequently passed PREA, which was signed into law on December 3, 2003.<sup>11</sup> Many of the provisions described under the pediatric rule were adopted under PREA. Under PREA as originally enacted and under its reauthorization under the Food and Drug Administration Amendments Act of 2007, a proposed timeline and plan for the submission of pediatric studies were not required to be submitted during the investigational new drug application (IND) phase of drug development.<sup>12</sup> Under FDASIA, signed into law on July 9, 2012, for the first time PREA includes a provision that requires manufacturers of drugs subject to PREA to submit a PSP early in the drug development process. The intent of the PSP is to identify needed pediatric studies early in drug development and begin planning for these studies. The timing and content of the submission of an initial PSP are described below. FDASIA requires the FDA to promulgate regulations and issue guidance to implement these and other provisions.<sup>13</sup> The FDA is issuing this guidance and intends to publish a proposed regulation consistent with FDASIA.

### **III. APPLICATIONS THAT REQUIRE SUBMISSION OF AN INITIAL PSP<sup>14</sup>**

A sponsor who is planning to submit a marketing application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration (i.e., that triggers PREA) is required to submit an initial PSP.<sup>15</sup> By statute, a biosimilar product that has not been determined to be interchangeable with the

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<sup>9</sup> See 21 CFR 312.47 and 312.82.

<sup>10</sup> *Association of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 222 (D.D.C. 2002)

<sup>11</sup> Public Law 108-155, 117 Stat. 1936 (Dec. 3, 2003)

<sup>12</sup> Public Law 110-85, 121 Stat. 823 (Sept. 27, 2007)

<sup>13</sup> See section 505B(e)(7) of the FD&C Act; 21 U.S.C. 355c(e)(7).

<sup>14</sup> See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1).

<sup>15</sup> See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1); and section 505B(a)(1) of the FD&C Act; 21 U.S.C. 355c(a)(1).

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reference product is considered to have a “new active ingredient” for purposes of PREA.<sup>16</sup> The sponsor should submit the initial PSP to the relevant drug’s IND for review by the Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) review division as appropriate. Sponsors should submit an initial PSP according to the time frame outlined in section IV., Timing of a PSP Submission.

### **IV. TIMING OF A PSP SUBMISSION**

A sponsor must submit the initial PSP before the date on which the sponsor submits the required assessments and not later than 60 calendar days after the date of the end-of-phase 2 meeting.<sup>17</sup> In the absence of an end-of-phase 2 meeting, the sponsor should submit the initial PSP as early as practicable but before the initiation of any phase 3 studies, or any combined phase 2 and phase 3 study, of the drug that is the subject of the initial PSP. If a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the initial PSP no later than 210 calendar days before a marketing application or supplement is submitted.<sup>18</sup> A sponsor should submit the initial PSP to its IND for the drug. In cases when there is no active IND for the drug, but the sponsor expects upon submission of the IND that the initial studies would include a phase 3 study, the initial PSP should be submitted as a pre-IND submission. In this situation, the FDA encourages sponsors to schedule a pre-IND meeting before submission of the initial PSP, and, as stated above, the sponsor should submit the initial PSP before the initiation of any phase 3 studies or combined phase 2 and phase 3 study.<sup>19</sup> See Appendix 1 for special considerations for new drug applications (NDAs), biologics license applications (BLAs), and efficacy supplements that trigger PREA submitted between January 5, 2013, and January 5, 2014.

### **V. CONTENTS OF THE INITIAL PSP**

The FD&C Act requires that an initial PSP include “(i) an outline of the pediatric study or studies that the sponsor plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); (ii) any request for a deferral, partial waiver, or waiver . . . if applicable, along with any supporting information; and

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<sup>16</sup> See section 505B(m) of the FD&C Act; 21 U.S.C. 355c(m).

<sup>17</sup> See section 505B(e)(2)(A) of the FD&C Act; 21 U.S.C. 355c(e)(2)(A).

<sup>18</sup> Section 505B(e)(2)(A) specifies the time frame for submission of an initial PSP if there is an end-of-phase 2 meeting or such other time as may be agreed upon between the FDA and the sponsor. The FDA expects to agree to time frames other than those specified in the text of this guidance only if there are exceptional circumstances. The appropriate component of CDER or CBER should be contacted should the sponsor believe exceptional circumstances exist.

<sup>19</sup> Information on the timing of submission of an initial PSP for biosimilar products can be found in the draft guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*. When final, this guidance will represent the FDA’s current thinking on this topic.

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(iii) other information specified in the regulations” promulgated by the FDA.<sup>20</sup> This section of the guidance describes information sponsors must or should submit in the initial PSP submission. In certain situations, it may be premature to include a detailed outline of a planned pediatric study (or studies) because additional data are needed (e.g., efficacy, safety, potential endpoints). In such cases, the outline of the pediatric studies should include a justification for not including more detailed information.

Appendix 2 provides a template that sponsors should complete with all information available at the time of the initial PSP submission.<sup>21</sup> The FDA acknowledges that the development program for a drug may change based on data collected from nonclinical studies, early phase clinical trials, and/or other clinical development programs. Therefore, sponsors should consider the current stage of the clinical development program for their specific drug at the time they complete the initial PSP template. Additionally, sponsors can submit amendments to an agreed-upon initial PSP at any time<sup>22</sup> if changes to the pediatric plan need to be considered based on additional data described above. Submission of amendments to an agreed-upon initial PSP are discussed in section VI., Contents of Requested Amendment to an Initial PSP.

Recommendations for the contents of each section of the initial PSP are detailed below.

### **1. Overview of the Disease Condition in the Pediatric Population**

This section should briefly summarize (1 to 5 pages) the pathophysiology of the disease, methods of diagnosis, and currently available treatments and/or prevention strategies in the pediatric population, including neonates. The sponsor should also include the incidence and prevalence of the disease in the overall population and the incidence and prevalence in the pediatric population.

### **2. Overview of the Drug or Biological Product**

This section should briefly summarize (1 to 5 pages) the proposed mechanism of action of the drug (to the extent understood) and describe the potential therapeutic benefits or fulfillment of therapeutic needs in the pediatric population, including neonates. A broad consideration of any possible therapeutic uses of the drug in children beyond the disease or indication being sought in adults may serve as the basis for a Written Request under section 505A of the FD&C Act (21 U.S.C. 355a). If a sponsor plans to submit a proposed pediatric study request asking the FDA to issue a Written Request in the future, that information should be included in the overview as appropriate.<sup>23</sup>

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<sup>20</sup> Section 505B(e)(2)(B) of the FD&C Act; 21 U.S.C. 355c(e)(2)(B)

<sup>21</sup> This template also is available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf>.

<sup>22</sup> Section 505B(e)(5) of the FD&C Act; 21 U.S.C. 355c(e)(5)

<sup>23</sup> For additional information regarding Written Requests, see section 505A of the FD&C Act; 21 U.S.C. 355a.



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### **3. Overview of Planned Extrapolation to Specific Pediatric Populations**

Extrapolation of efficacy from adult populations to pediatric populations may be appropriate if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients.<sup>24</sup> Extrapolation of efficacy from one pediatric age group to another pediatric age group also may be appropriate.<sup>25</sup> However, if a clear understanding of exposure-response in adults that can be applied to pediatrics (or from one pediatric age group to another) has not yet been established, the ability to extrapolate efficacy may not be known at the time of the PSP submission.

When determining whether the data are sufficient or will be used to support extrapolation of efficacy, sponsors should include information in the PSP on the similarities (and differences) between adults and children (or between one pediatric age group and another) in disease pathogenesis, criteria for disease definition, clinical classification, and measures of disease progression, as well as pathophysiologic, histopathologic, and pathobiological characteristics of the disease.

This section should address any plans to extrapolate efficacy from adult to pediatric patients or from one pediatric age group to another (1 to 5 pages). The sponsor should consider all age ranges of pediatric patients, including neonates. The sponsor should provide justification for the extrapolation, including any available supporting data for all age groups for which efficacy will be extrapolated. This justification should include supportive data from all available sources (e.g., sponsor data, published literature, expert panels, and workshops). Extrapolation of efficacy for other drugs in the same class, if previously accepted by the FDA, also can be considered supportive information.<sup>26</sup>

### **4. Request for Drug-Specific Waiver(s)**

This section should discuss the plans to request a waiver (either full or partial) of the requirement to provide data from pediatric studies based on the above criteria (1 to 3 pages). The sponsor should provide justification with a summary of supporting data, for all age groups for which the waiver will be sought. Supportive data should include data from all relevant sources, including sponsor data, published literature, expert panels and workshops, and consensus documents. Full or partial waivers previously granted for other drugs in the same class can be considered supportive information. It should be noted that requested waivers in the PSP will not be formally granted or denied until the application is approved.<sup>27</sup>

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<sup>24</sup> Section 505B(a)(2)(B)(i) of the FD&C Act; 21 U.S.C. 355c(a)(2)(B)(i)

<sup>25</sup> Section 505B(a)(2)(B)(ii) of the FD&C Act; 21 U.S.C. 355c(a)(2)(B)(ii)

<sup>26</sup> Additional information on extrapolation can be found in section IV.C. of the draft guidance for industry *How to Comply With the Pediatric Research Equity Act*.

<sup>27</sup> Additional information on waiver requests can be found in section VI. of the draft guidance for industry *How to Comply With the Pediatric Research Equity Act*.

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If studies will be waived because there is evidence that the drug would be ineffective or unsafe in any pediatric age group, this information must be included in the product labeling.<sup>28</sup> Generally, this information would be included in the *Pediatric Use* subsection of labeling.

### 5. Summary of Planned Nonclinical and Clinical Studies

This section should include a summary in tabular form of all planned: (1) nonclinical studies (if existing nonclinical data are not sufficient to support the proposed clinical trials; see section 7); and (2) clinical pediatric studies (categorized by age). Any age groups for which the sponsor will request waivers also should be included in this table along with a column to identify whether the sponsor will request a deferral of the study (i.e., the data are not planned to be submitted until after the application is approved). A sample table is included below. It should be noted that the table is provided as an example only. The specific studies planned for a specific drug (e.g., the type of studies and the age groups studied) may differ from those studies listed in the sample table.

**SAMPLE TABLE: Table of Nonclinical and Clinical Studies for Drug X**

PLANNED NONCLINICAL STUDIES*			
Species	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)**
Rat (or appropriate animal species)	Toxicology study in juvenile animals	To support initiation of clinical studies in children ages x – xx	N
PLANNED PEDIATRIC CLINICAL STUDIES			
Pediatric PK Studies <sup>+</sup>			
Age Group	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)
1-<17 years	Phase 2 PK/PD study <sup>+</sup>	To determine appropriate dose based on an established PD endpoint	N
Clinical Effectiveness and Safety Studies			
Age Group	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)
0-1 year	Waiver requested	Studies are highly impracticable	
1-6 years	Efficacy study (R, DB, PC) <sup>+</sup>	Endpoints to be determined	Y
6-12 years	Efficacy study (R, DB, PC)	Endpoints to be determined	Y
12-<17 years	Efficacy study (R, DB, PC)	Study to be submitted with initial NDA	N

\* May not be applicable for all drugs.

\*\* See section 11 of the Initial Pediatric Study Plan Template.

<sup>+</sup> PK = pharmacokinetics; PD = pharmacodynamics; R = randomized; DB = double-blind; PC = placebo-controlled

<sup>28</sup> Section 505B(a)(4)(D) of the FD&C Act; 21 U.S.C. 355c(a)(4)(D)

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### **6. Pediatric Formulation Development**

This section should provide details of any pediatric-specific formulation development plans, if appropriate, including whether the formulation that is being developed can be used for all pediatric populations (1 to 3 pages). If the current formulation is not suitable for all pediatric age groups, sponsors should provide specific plans for the development of an age-appropriate formulation for all pediatric age groups that will be studied. Sponsors should include information regarding planned excipients, to the extent practicable, which will be contained in a pediatric formulation. Sponsors also should provide details about the size of all planned capsules or tablets, to the extent practicable, to be used in pediatric studies.<sup>29</sup>

### **7. Nonclinical Studies**

This section should provide a brief summary (1 to 5 pages) of the data from relevant nonclinical studies that support the use of the drug in all pediatric age groups the sponsor will study in the proposed clinical trials. The sponsor should include information that supports the maximum dose and duration of treatment to be used in pediatric studies. If additional nonclinical studies are **not** planned, the rationale for this decision should be included.

If the existing nonclinical data are not sufficient to support the proposed clinical trials, sponsors should provide a brief description for each of the studies they will conduct, including, at a minimum:

- The species to be studied
- The age of animals at start of dosing
- Duration of dosing
- Target organ systems of concern with key developmental endpoints to be evaluated

These studies should be listed in the table in section 5.

### **8. Clinical Data to Support Design and/or Initiation of Studies in Pediatric Patients**

This section should provide a brief summary (1 to 5 pages) of any clinical data that support the design and/or initiation of pediatric studies. This section also can include available data in adult or pediatric patients who have received treatment with the drug (or related drugs) for the proposed indication, for other conditions, or in earlier studies.

### **9. Planned Pediatric Clinical Studies**

#### **9.1 Pediatric Pharmacokinetic Studies**

This section should provide an outline of each of the pediatric pharmacokinetic/pharmacodynamic (PK/PD) study (or studies) planned, if applicable (1 to 10 pages). The studies

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<sup>29</sup> Additional information on formulation development can be found in section V.C. of the draft guidance for industry *How to Comply With the Pediatric Research Equity Act*.

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should be discussed in the order they are presented in the table in section 5. For each study, to the extent practicable, the sponsor should address the following:

- Type of study/study design
- Objectives of study
- Age group and population in which the study will be conducted
- Pediatric formulation(s) used in this study
- Dose ranges to be used in the PK studies
- Endpoints and justification (PK parameters; PD biomarkers)
- Existing or planned modeling and simulation to support dose selection and/or study design for the pediatric studies
- Any planned pharmacogenomic analyses
- Sample size justification

### **9.2 Clinical Effectiveness and Safety Studies**

This section should provide an outline of each pediatric study planned, discussed in the order they are presented in the table in section 5 (1 to 10 pages). For each study, to the extent practicable, the sponsor should address the following:

- Type of study/study design
- Objectives of the study
- Age group and population in which the study will be conducted
- Inclusion and exclusion criteria for the study
- Endpoints (primary and key secondary) to be used
- Timing of endpoint assessments
- Safety assessments (including timing and length of follow-up)
- Statistical approach (e.g., statement of null and alternative hypotheses, sample size/power justification)

### **10. Timeline of the Pediatric Development Plan**

Each study listed in the table in section 5 should include a general timeline for completion of the study in this section (1 to 2 pages). A suggested template is provided below. The sponsor should estimate these dates based on current projections for the drug development program. If the dates provided in the initial PSP change as drug development proceeds, the sponsor should submit a request to amend the initial PSP. Furthermore, the request should include justification for the change in the dates provided below for amendment of the initial PSP.<sup>30</sup>

1. Formulation development, if applicable
2. Nonclinical studies, if applicable

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<sup>30</sup> See section 505B(e)(5) of the FD&C Act; 21 U.S.C. 355c(e)(5).

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### 3. Clinical studies

- PK studies, if applicable:
  - Estimated protocol submission date: No later than \_\_\_\_ (month/year)
  - Estimated study initiation date: No later than \_\_\_\_ (month/year)
  - Estimated final report submission date: No later than \_\_\_\_ (month/year)
- Efficacy/safety studies
  - Estimated protocol submission date: No later than \_\_\_\_ (month/year)
  - Estimated study initiation date: No later than \_\_\_\_ (month/year)
  - Estimated final report submission date: No later than \_\_\_\_ (month/year)

### 4. Target date of application submission

## **11. Plan to Request Deferral of Pediatric Studies**

Sponsors may request deferral of pediatric assessments.<sup>31</sup> The initial PSP should include any plans to request deferral of pediatric assessments in some or all pediatric groups until after approval of a future application (or supplement) in other age groups. If new information, such as data from ongoing or planned studies, indicates that a criterion for a waiver (or partial waiver) is met, planned requests for deferral of pediatric assessments in the initial PSP can be changed to planned requests for waiver (or partial waiver). These changes should be submitted as an amendment to an agreed-upon initial or amended PSP.

For any studies listed in the table in section 5 of planned nonclinical and clinical studies that will not be submitted as part of a planned application (i.e., NDA, BLA, or efficacy supplement), sponsors must submit any request for a deferral.<sup>32</sup> The FDA may grant a deferral of required pediatric studies if it finds that: (1) the drug or biological product is ready for approval for use in adults before pediatric studies are complete; (2) pediatric studies should be delayed until additional safety or effectiveness data have been collected; or (3) there is another appropriate reason for deferral.<sup>33</sup> The planned request for a deferral should be listed in the order of the proposed studies in the table in section 5, and should include adequate justification and any currently available evidence justifying the request for a deferral (1 to 2 pages). It should be

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<sup>31</sup> Under PREA, a pediatric assessment “shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate (i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and (ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective.” Section 505B(a)(2)(A) of the FD&C Act; 21 U.S.C. 355c(a)(2)(A).

<sup>32</sup> Section 505B(e)(2)(B)(ii) of the FD&C Act; 21 U.S.C. 355c(e)(2)(B)(ii)

<sup>33</sup> Section 505B(a)(3) of the FD&C Act; 21 U.S.C. 355c(a)(3). In addition, the sponsor must submit: (1) a certification of the grounds for deferring the assessments; (2) a pediatric study plan; (3) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and (4) a timeline for the completion of such studies. Section 505B(a)(3)(A)(ii) of the FD&C Act; 21 U.S.C. 355c(a)(3)(A)(ii).

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noted that requested deferrals in the initial PSP will not be formally granted or denied until the drug is approved.<sup>34</sup>

### **12. Agreements for Other Pediatric Studies**

Sponsors should include, if available, a summary (1 to 5 pages) of the agreed-upon pediatric investigation plan with other regulatory authorities (e.g., European Medicines Agency). If negotiations with a regulatory authority are in progress, a summary of the draft plan should be included. A summary of any agreements with other regulatory authorities also should be included. A summary of any clinical investigation conducted under an IND for an indication other than the indication that is the subject of the initial PSP also should be included.

## **VI. CONTENTS OF REQUESTED AMENDMENT TO AN INITIAL PSP**

As stated above, sponsors can request to amend an agreed-upon initial PSP at any time, if, for example, changes to the milestone submission dates occur, planned requests for a deferral change to planned requests for a waiver or partial waiver, or if a plan for a waiver or partial waiver will change to a deferral. A request for an amendment to an agreed-upon initial PSP should include:

- Specifications of the requested change(s), along with a justification and an assessment of the effect of both making and failing to make the proposed change(s)
- A copy of the agreed-upon initial PSP with the requested change(s) shown in red
- A clean copy of the amended PSP

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<sup>34</sup> Additional information on deferral requests can be found in section VI. of the draft guidance for industry *How to Comply With the Pediatric Research Equity Act*.

*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

**APPENDIX 1:  
SPECIAL CONSIDERATIONS FOR NDAs, BLAs, AND  
EFFICACY SUPPLEMENTS SUBMITTED BETWEEN  
JANUARY 5, 2013, AND JANUARY 5, 2014**

If a sponsor submits an NDA, BLA, or efficacy supplement that triggers PREA before **January 5, 2014**, the FDA intends to exercise enforcement discretion with regard to the new provisions found in FDASIA that require an agreed-upon initial PSP be submitted as part of the application.<sup>35</sup> However, the FDA encourages sponsors who are planning to submit such an application before January 5, 2014, to submit an initial PSP for review as soon as possible. Sponsors should be aware that review of and agreement to an initial PSP generally will require at least 7 months. If an agreed-upon initial PSP is not included in the application, the sponsor should submit a description of the planned or ongoing studies as previously required under PREA.<sup>36</sup>

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<sup>35</sup> Pediatric assessments required under 505B(a)(2) of the FD&C Act, however, must be submitted regardless of the date the application is filed. The FDA does not intend to exercise enforcement discretion with regards to the submission of these assessments.

<sup>36</sup> For additional information on the previous requirements under PREA, see the draft guidance for industry *How to Comply With the Pediatric Research Equity Act* and the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85), section 402.

**APPENDIX 2:  
INITIAL PEDIATRIC STUDY PLAN TEMPLATE<sup>37</sup>**

- 1. OVERVIEW OF THE DISEASE IN THE PEDIATRIC POPULATION (1-5 pages)**
- 2. OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT (1-5 pages)**
- 3. OVERVIEW OF PLANNED EXTRAPOLATION TO SPECIFIC PEDIATRIC POPULATIONS (1-5 pages)**
- 4. REQUEST FOR DRUG-SPECIFIC WAIVER(S) (1-3 pages)**
- 5. SUMMARY OF PLANNED NONCLINICAL AND CLINICAL STUDIES**
- 6. PEDIATRIC FORMULATION DEVELOPMENT (1-3 pages)**
- 7. NONCLINICAL STUDIES (1-5 pages)**
- 8. CLINICAL DATA TO SUPPORT DESIGN AND/OR INITIATION OF STUDIES IN PEDIATRIC PATIENTS (1-5 pages)**
- 9. PLANNED PEDIATRIC CLINICAL STUDIES**
  - 9.1 Pediatric Pharmacokinetic Studies (1-10 pages)**
  - 9.2 Clinical Effectiveness and Safety Studies (1-10 pages)**
- 10. TIMELINE OF THE PEDIATRIC DEVELOPMENT PLAN (1-2 pages)**
- 11. PLAN TO REQUEST DEFERRAL OF PEDIATRIC STUDIES (1-2 pages)**
- 12. AGREEMENTS FOR OTHER PEDIATRIC STUDIES (1-5 pages)**

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<sup>37</sup> This template is also available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf>.